American Journal of Hematology 58:84–86 (1998)

Transfusion-Associated Graft-Versus-Host Disease in Immunocompetent Patient: Early Diagnosis and Therapy

Masahiro Sakurai,[1]* Yoshimasa Moizumi,[2] Shigeharu Uchida,[3] Yoshimichi Imai,[2] and Koichi Tabayashi[1]

[1]Department of Thoracic and Cardiovascular Surgery, Tohoku University School of Medicine, Sendai, Japan
[2]Department of Thoracic and Cardiovascular Surgery, Sendai Medical Center, Sendai, Japan
[3]Department of Research, The Japanese Red Cross Central Blood Center, Tokyo, Japan

We report a case of transfusion-associated graft-versus-host disease in a previously healthy, 68-year-old Japanese man following an emergency surgery for an acute aortic dissection. We confirmed the chimerism of lymphocytes and the effect of drug therapy using DNA polymorphism analysis. This method is a sensitive, convenient, and rapid method that it is also useful for the evaluation of therapy. And the combination therapy with methylprednisolone, cyclosporine, and 15-deoxyspergualin may be effective in treating transfusion-associated GVHD. Am. J. Hematol. 58:84–86, 1998. © 1998 Wiley-Liss, Inc.

Key words: TA-GVHD; polymorphism analysis of microsatellite DNA; 15-deoxyspergualin

INTRODUCTION

Transfusion-associated graft-versus-host disease (TA-GVHD) occurs in 0.15% of immunocompetent patients who undergo cardiovascular surgery in Japan [1–3]. High incidence is believed to be related to the transfusion of fresh blood during cardiovascular surgery, and the frequency of the Japanese population sharing one identical haplotype [1]. Diagnosis in early stage is difficult, and no effective treatment for TA-GVHD has been established, thus the disorder is usually fatal [1,3,4]. We present our experience in diagnosing and treating a patient with this disease.

CASE REPORT

A 68-year-old Japanese man without previous medical illness received 20 U of a filtered (leukocyte reduction filter, TLX 10-A W, Asahi Medical, Tokyo, Japan) platelet concentrate, which was drawn from 4 donors, during emergency surgery for an acute aortic dissection (De Bakey-I). Postoperatively, his recovery was excellent with all his routine laboratory data in normal ranges until the postoperative day 13, when he developed fever, diarrhea, and liver dysfunction. On day 14, an erythematous rash appeared over his entire body. Leukopenia, thrombocytopenia, and a persistent metabolic acidosis also developed. On day 15, his platelet count was $3 \times 10^4/mm^3$, RBC $286 \times 10^4/mm^3$, and WBC $1.5 \times 10^3/mm^3$. CD-8 positivity was detected as 75% of peripheral blood mononuclear cells. Serologic tests for hepatitis and antinuclear antibodies were found negative. Examination of a skin biopsy specimen, showing an early separation of the dermal-epidermal junction, basal apoptosis, mild mononuclear cell inflammatory reaction migrating into the epidermis, and scattered necrotic keratinocytes, suggested the diagnosis of GVHD. Polymorphism analysis of microsatellite DNA from the fingernail and blood samples in our previous report [5] obtained on day 16, showed the same band that had been detected in donor samples of D6S89, HGH, APOCIII (data not shown), and ACTBP2 locus (Fig. 1, lane 2: DNA from patient's fingernail specimen on day 16; lane 3: DNA from patient's peripheral blood cells on day 16; lane 5: DNA from donor's peripheral blood cells). The patient was treated daily with 16 mg/kg of methylprednisolone, 89 mg/kg of cyclosporine, and 3 mg/kg of 15-deoxyspergualin. By the 3rd day after the start of therapy the clinical symptoms of fever, erythematous rash, diarrhea, and metabolic acido-

*Correspondence to: Masahiro Sakurai, MD, Department of Thoracic and Cardiovascular Surgery, Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-77, Japan.

Received for publication 25 July 1997; Accepted 10 December 1997

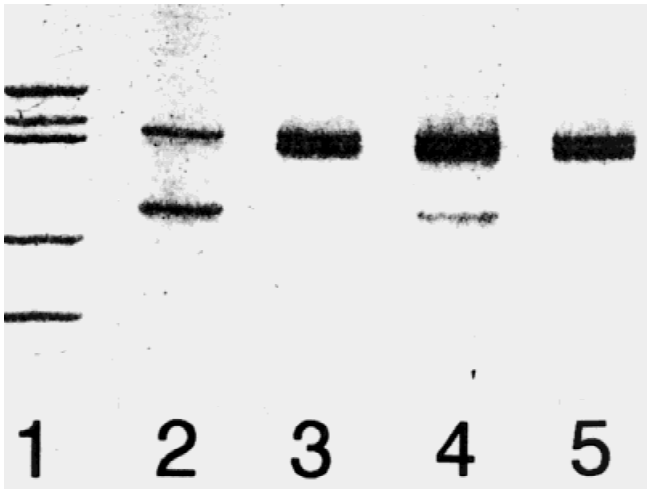

Fig. 1. Results of DNA polymorphism analysis of the ACTBP2 locus in a patient with transfusion-associated GVHD. Lane 1: DNA size marker ØX174 digested with Hae III; lane 2: PCR products from the specimen of patient's fingernail clippings; lane 3: PCR products from patient's peripheral blood cells after blood transfusion; lane 4: PCR products from patient's peripheral blood cells after administration of methylprednisolone, cyclosporine, and 15-deoxyspergualin; lane 5: PCR products from the donor's peripheral blood cells.

sis had improved, and the skin biopsy showed normal findings. On day 19, DNA polymorphism analysis showed a mixed pattern of the patient-derived band and the donor-derived bands, though the donor-derived DNA was predominant (Fig. 1, lane 4: DNA from patient's peripheral cells on day 19). The patient unfortunately died of sudden cardiac arrest on day 20. An autopsy was not performed.

DISCUSSION

TA-GVHD can usually be diagnosed clinically during its florid stage. However, in its early stage, it is not easy to distinguish from toxic shock syndrome, drug reactions, or viral infections. Early diagnosis of TA-GVHD may allow more effective treatment of the disease. Definitive evidence of TA-GVHD relies on the demonstration of circulating lymphocytes with an HLA type that is different from that of the host cells. Unfortunately, often HLA typing cannot identify the donor's lymphocytes in a patient with TA-GVHD due to lymphopenia. In the past few years, the use of restriction-fragment-length polymorphisms (RFLPs) and DNA probes to detect mixed hematopoietic and chimeric states have been demonstrated and reported [6]. However, these methods are problematic and often detect relatively uninformative variations in DNA sequences [5]. The method of the polymorphism analysis of microsatellite DNA associated with variations in length of microsatellite repeats can identify donor DNA in patients with TA-GVHD and has the advantages of speed, sensitivity, and easy analysis [5].

We confirmed the chimerism of lymphocytes and effect of drug therapy using DNA polymorphism analysis. This method of the polymorphism analysis of microsatellite DNA associated with variations in length of microsatellite repeats can identify donor DNA in patients with TA-GVHD, and has the advantages of speed, sensitivity, and ease of analysis that is also useful for the evaluation of therapy [5].

Cyclosporin and methylprednisolone combination is the most widely used immunosuppressants for GVHD. However, these agents are not always effective in controlling GVHD. A previous study had shown that 15-deoxyspergualin was effective in a patient with cyclosporine- and steroid-resistant GVHD after a bone marrow transplantation [8]. 15-deoxyspergualin has been found to be effective against lethal GVHD in animal models [9]. However, its mode of action could not be fully explained. It has also been reported that 15-deoxyspergualin abolishes the activity of cytotoxic T lymphocytes [10].

We treated our patient with a combination of methylprednisolone, cyclosporine, and 15-deoxyspergualin, which was used as a T-cell cytotoxic regimen. Three days after the start of this combination therapy, a definite improvement in clinical symptoms was observed, and the polymorphism analysis of microsatellite DNA following the therapy also verified the effect of our drug combination on the disease.

Our study is the first report on the triple drug therapy for the treatment of TA-GVHD. The present result suggests that a combination therapy with methylprednisolone, cyclosporine, and 15-deoxyspergualin may be effective in treating TA-GVHD.

ACKNOWLEDGMENTS

We thank Dr. K. Tadokoro and Dr. H. Okazaki for their helpful discussion.

REFERENCES

1. Takahashi K, Juji T, Miyamoto M, Uchida S, Akaza T, Tadokoro K, Shibata Y, Ino T, Hidano A, and the Japanese Red Cross PT-GVHD Study group: Analysis of risk factors for post-transfusion graft-versus-host disease in Japan. Lancet 343:700–702, 1994.
2. Sakakibara T, Juji T: Post-transfusion graft-versus-host disease after open heart surgery. Lancet 2:1099, 1986.
3. Juji T, Takahashi K, Shibata Y, Ide H, Sakakibara T, Ino T, Mori S: Post-transfusion graft versus host disease in immunocompetent patient after cardiac surgery in Japan. N Engl J Med 321:56, 1989.
4. Mast BJ, Hornstra N, Ruigrok MB, Class FHJ, Rood JJ, Lagaaij EL: Transfusion-associated graft-versus-host disease in immunocompetent patients: A self-protective mechanism. Lancet 343:753–757, 1994.

5. Wang Li, Juji T, Tokunaga K, Takahashi K, Kuwata S, Uchida S, Tadokoro K, Takai K: Brief report: Polymorphic microsatellite markers for the diagnosis of graft-versus-host disease. N Engl J Med 330:398–401, 1994.
6. Petz LD, Calhoun L, Yam P, Cecka M, Schiller G, Faitlowicz AR, Herron R, Sayah D, Wallace RB, Belldegrun A: Transfusion-associated graft-versus-host disease in immunocompetent patients: Report of a fatal case associated with transfusion of blood from a second-degree relative, and a survey of predisposing factors. Transfusion 33: 742–750, 1993.
7. Uchida S, Wang L, Yahagi Y, Tokunaga K, Tadokoro K, Juji T: Utility of fingernail DNA for evaluation of chimerism after bone marrow transplantation and for diagnostic testing for transfusion-associated graft-versus-host disease. Blood 87:4015–4016, 1996.
8. Kasai M, Hiba T, Naohara T, Masazui N, Watanabe M, Matsuura A, Ohizumi H, Tanaka J, Morii K, Kiyama Y, Saitoh M, Hashio S, Kobayashi H, Kobayashi M, Imamura M, Sakurada K, Miyazaki T: 15-deoxyspergualin controls cyclosporin- and steroid-resistant intestinal acute graft-versus-host disease after allogeneic bone marrow transplantation. Bone Marrow Transplant 14:315–317, 1994.
9. Neomoto K, Hayashi M, Ito J, Sugawara Y, Mae T, Fujii H, Abe F, Fujii A, Takeuchi T: Deoxyspergualin in lethal murine graft-versus host disease. Transplantation 51:712–715, 1991.
10. Nemoto K, Sugawara Y, Mae T, Hayashi M, Abe F, Takeuchi T: Immunological unresponsiveness by deoxyspergualin therapy in mice undergoing lethal graft-vs-host disease, and successful adoptive transfer of unresponsiveness. Transplant Proc 23:862–863, 1991.